Remarks

Claim 1 is amended to incorporate the limitations of claims 2 and 16. Claims 4-6 and 31 are amended herein to depend from claim 1. Claim 25 is amended herein to include limitations from claims 1, 2 and 6. Claim 27 is amended to correct form.

New claims 35-39 added herein. Support for new claims 35-39 can be found throughout the specification, including but not limited to, pages 22-33 and page 45.

Claims 2, 15-17, 28, 30 and 32-34 are canceled herein.

No new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Each of the rejections raised under 35 U.S.C. § 103(a) is addressed in detail below.

I. Claims 1, 2, 6, 8-15, 21, 22, 26, 27 and 31 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al. (PCT Publication No. WO 00/61151), Lu et al. (Vaccine, 1997) and Cho et al. (Nature Biotechnology, 2000). Applicants respectfully disagree with this rejection as applied to the claims as amended.

A. The Prior Art Does Not Teach All of the Elements of the Claimed Methods

The Office action acknowledges that Klinman et al. does not teach a methods for increasing an immune response to an opportunistic infection in an *immunocompromised subject having SIV or AIDS* (see the paragraph bridging pages 5-6 of the Office action). Thus, Klinman et al. cannot possible teach methods for increasing an immune response to a *Leishmania* infection in an immunocompromised subject infected with HIV or SIV.

Klinman et al. teach immunostimulatory K-type ODNs that include at least about 10 nucleotides and include a sequence represented by the formula:

$$5' \ N_1N_2N_3T\text{-}CpG\text{-}WN_4N_5N_6 \ 3'$$

wherein the central CpG motif is unmethylated, W is A or T, and N_1, N_2, N_3, N_4, N_5, and N_6 are any nucleotides. The specification describes these ODNs at page 22, lines 15-21. K-type ODNs stimulate B cell proliferation and the secretion of IgM and IL-6 and affect humoral immunity. As discussed in the specification, K ODNs are different from D ODNs (see the specification, pages 22-28.

Klinman et al. also describe a broad class of D ODNs of the formula:

5' RY-CpG-RY 3'

wherein the central CpG motif is unmethylated, R is A or G (a purine), and Y is C or T (a pyrimidine). The present specification describes these ODNs on page 23, lines 24-27. These ODNs can be 100 nucleotides in length or less, such as 10-75 nucleotides or 50 nucleotides or less. The nucleic acid sequence set forth as SEQ ID NO: 177, which is one member of the large class of ODNs, is disclosed in Klinman et al.

However, the presently claimed methods are directed to the use of a specific *subset* of D ODNs to increase an immune response to a *Leishmania* infection in an *immunocompromised subject with an HIV or an SIV infection*. The use this specific subset of ODNs, namely, ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the following formula:

5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22)

wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 10, simply cannot be construed to be suggested, or render obvious by Klinman et al.

Lu *et al.* teaches vaccination of healthy animals with a plasmid vaccine encoding SIVmac proteins. The healthy animals were subsequently challenged with SIV, in order to prevent the SIV infection. Some of the vaccinated animals, in addition to the unvaccinated animals, developed secondary pneumonia, Epstein-Barr Virus (EBV) infections, Tuberculosis infections or Trichomonas infections following SIV challenge. Lu *et al.* do not disclose an infection with *Leishmania* secondary to SIV infection.

Lu et al. do not describe any therapeutic interventions for the treatment of secondary infections, and cannot be construed to suggest any increase the immune response in these

animals using any means. In fact, Lu et al. disclose that secondary infections occurred in animals that maintained their CD4 count, and that secondary infections occurred in one animal that had high and persistent Gag-specific responses (see page 923). Thus, Lu et al. does not make up for the deficiencies of Klinman et al.

Cho *et al.* describe vaccination of healthy animals with an immunostimulatory DNA sequence conjugated to ovalbumin and evaluating CTL activity and cytokine production in response to the vaccine. Animal receiving the vaccine were protected against a lethal burden of OVA-expressing tumor cells. None of the experiments performed by Cho et al. utilized immunocompromised animals, let alone subjects infected with an immunodeficiency virus. Furthermore, as the animals used in the experiments described by Cho et al. were healthy, they could not have had any infections (including secondary infections). Cho *et al.* merely postulate that a vaccine comprising an immunostimulatory DNA sequence could be used to induce protective immunity, such as to produce an immune response to HIV itself (see page 513). However, there is no teaching or suggesting in Cho et al. that immunostimulatory DNAs could be used to produce an immune response to a secondary infection, let alone a *Leishmania* infection.

Thus, there is nothing in Klinman et al., Lu et al. or Cho et al. alone or in any combination, that teaches the following elements:

1. Treatments to produce an immune response against a secondary infection in a subject that is immunocompromised as a result of an HIV or an SIV infection.
2. The production of an immune response to *Leishmania* in any subject (including immunocompromised subjects).
3. The use of a subset of immunostimulatory ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1, to induce the immune response in a immunocompromised subject.

Thus the prior art simply does not teach each element of the claimed methods (see MPEP § 2143). No *prima facie* case of obviousness has been made with regard to the claims as amended.

B. The Documentation of an Unexpected Superior Result Overcomes a Prima Facie Case of Obviousness

Even if the rejection is inappropriately maintained, the claimed methods provide unexpectedly superior results, as discussed at length in the Declaration under 37 C.F.R. § 1.132 (submitted with the response filed on June 5, 2008, hereinafter "the Declaration"), the response filed January 2, 2009, the response filed o July 17, 2009 and the response filed on January 4, 2010. For the Examiner's convenience, some of the prior arguments are summarized below.

Pages 4-5 of the Declaration describe the results obtained when D oligodeoxynucleotides were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected for greater than 12 months with SIV Mac239, and had viral loads ranging from 0.3-28 x 10^6 copies/ml, were used in these studies. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin). Healthy macaques challenged with *L. major* developed cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days after challenge and resolved within 50 days (see Fig. 3A of the Declaration). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K oligodeoxynucleotide (ODN) was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with D ODN (see presently pending claim 1) developed significantly smaller lesions, and their infection did not progress over time (Fig. 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a 35-fold reduction in total parasite burden at the lesion site compared to SIV-infected animals treated with control ODN or saline (see Fig. 3B of the Declaration, $p<0.001$). The comparative data, both with regard to the type of ODN used (D versus K), and the type of immune response achieved (general response versus a response to a secondary infection) demonstrate the unexpectedly superior result that is achieved using the claimed methods.

Verthelyi et al., J. Immunol. 170: 4717-4723, 2003 (of record, submitted on October 1, 2007) provides additional evidence of the superior results achieved with the claimed methods. This post-filing date publication provides additional evidence that D ODNs, specifically D19 (SEQ ID NO: 176), D35 (SEQ ID NO: 177), and D29 (SEQ ID NO: 178) can be used to induce an immune response to *Leishmania* in macaques infected with an immunodeficiency virus (SIV). Macaques treated with the D ODNs developed significantly smaller lesions, and their infection did not progress over time. However, the severity of *Leishmania* infection in animals treated with immunostimulatory K ODNs was not significantly different than controls. Monkeys treated with D ODN had a 35-fold reduction in parasite burden at the lesion site. This provides additional evidence of the unexpected superior results achieved using the claimed methods.

The documentation of an unexpectedly superior result overcomes any *prima facie* case of obviousness based on the cited references.

Reconsideration and withdrawal of the rejection are respectfully requested.

II. Claims 5 and 30 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al., Lu et al. and Cho et al. and further in view of Yilma (U.S. Patent No. 6,326,007) and Bielorai et al. (Bone Marrow Transplantation, 2000). Claim 30 is canceled herein. Applicants respectfully disagree with this rejection as applied to claim 5 as amended.

A. The Prior Art Does Not Teach All of the Elements of the Claimed Methods

Klinman et al., Lu et al. and Cho et al. are discussed above.

Yilma teaches that HIV-2 is associated with immunodeficiency and is also associated with susceptibility to secondary infections.

Bielorai et al. describes chronic granulomatosus disease as a primary immunodeficiency disorder, and discloses that subjects with this disease are susceptible to bacterial and fungal infections.

Yilma and Bielorai et al. do not make up for the deficiencies of Klinman et al., Lu et al. and Cho et al. There simply is nothing in any of Klinman et al., Lu et al., Cho et al., Yilma or Bielorai et al, alone or in any combination, that teach the following elements:

1. Treatments to produce an immune response against a secondary infection in a subject that is immunocompromised as a result of an HIV or an SIV infection.

2. The production of an immune response to *Leishmania* in any subject (including immunocompromised subjects).
3. The use of a subset of immunostimulatory ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M$ $(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1, to induce the immune response in a immunocompromised subject.

Thus the prior art simply does not teach each element of the claimed methods (see MPEP § 2143). No *prima facie* case of obviousness has been made with regard to the claims as amended.

B. The Documentation of an Unexpected Superior Result Overcomes a Prima Facie Case of Obviousness

The documentation of unexpectedly superior results, as discussed above, overcomes any *prima facie* case of obviousness that could possibly be made based on the cited references.

Reconsideration and withdrawal of the rejection are respectfully requested.

III. Claims 4, 16, 25, 28, 29 and 32 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al., Lu et al. and Cho et al. and further in view of Raz (U.S. Patent No. 6,552, 006), Hamour et al. (J. Infect., 1998 Abstract Only) and Glaser et al. (Clin. Infect. Dis., 1994 Abstract Only). Claims 16, 28 and 32 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this rejection as applied to claims 4, 25, 29 and 32 as amended.

A. The Prior Art Does Not Teach All of the Elements of the Claimed Methods

Klinman et al., Lu et al. and Cho et al. are discussed above.

Raz teaches the use of K-type ODNs for the treatment of *Mycobacterium* infections. Raz et al. disclose that in a murine leishmaniasis model, K-type ODNs increased serum IL-12.

The Hamour et al. abstract discloses that visceral Leishmania is an opportunistic infection in subjects with an HIV-1 infection. The Hamour et al. abstract describe treatment with amphotercin B, and suggest that amphoericin B could be used in combination therapeutics.

The Glaser et al. abstract teach that a number of opportunistic infections occur in subjects infected with HIV. It is concluded that the benefit of animal companionship outweigh the risks of animal ownership.

There is nothing in any of Klinman et al., Lu et al., Cho et al., Raz, Glaser et al. or Hamour et al. that teaches the specific selection of a subset of immunostimulatory ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1, to induce the immune response in a immunocompromised subject for the treatment of a *Leishmania* infection.

Klinman et al. merely teaches the differences between certain D and K ODN, and teaches the use of either type of ODN for immunostimulation. However, Raz et al. teach the production of IL-12 by K ODN is important for the treatment of *Leishmania* (albeit not in immunocompromised subjects), and teaches that K-type ODN are specifically of use to treat infections with intracellular pathogens. Lu et al. merely teaches that secondary infections develop in immunocompromised subjects, and Cho et al. describe effects of immunostimulatory DNA on inducing an immune response to tumors. Thus, in combination, these references merely suggest the use of K-type ODN to induce an immune response to a secondary infection.

The Glaser et al. abstract describes that opportunistic infections occur in subjects with HIV, but does not suggest the use of immunostimulatory ODNs at all. The Hamour et al. abstract describes treating Leishmania infections in subjects with HIV-1 using amphoericin B and another agent. Thus, one of skill in the art, upon combining all these references, might merely use a K-type ODN and amphoericin.

However, none of the references teach alone or in combination the selection and administration of a subset of D-type ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a

purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1. While SEQ ID NO: 177 is one ODN that falls into the broad genus of D-type ODNs discussed in Klinman et al., the mere disclosure of this nucleic acid amongst hundreds of ODNs (both D and K type) does not provide any motivation to select and use this particular ODN in an HIV or SIV infected subject to induce an immune response to *Leishmania*. In fact, as Raz teaches that K-type ODNs are effective for the treatment of *Leishmania*, upon combining these references, one of skill in the art would select and use the K-type ODNs described by Klinman et al.

Klinman et al., Lu et al. and Cho et al., Raz, the Hamour et al. abstract and Glaser et al. abstract, alone or in any combination simply do not teach each element of the claimed methods (see MPEP § 2143). No *prima facie* case of obviousness has been made with regard to the claims as amended.

B. The Documentation of an Unexpected Superior Result Overcomes a Prima Facie Case of Obviousness

The documentation of unexpectedly superior results, as discussed above, overcomes any *prima facie* case of obviousness that could possibly be made based on the cited references. As discussed above, macaques treated with the D ODNs developed significantly smaller lesions, and their infection did not progress over time. However, the severity of *Leishmania* infection in animals treated with immunostimulatory K ODNs (such as those described in Raz or in Klinman et al.) was not significantly different than controls. Monkeys treated with D ODN had a 35-fold reduction in parasite burden at the lesion site. This effect simply could not be predicted based on the cited prior art.

The documentation of unexpectedly superior results, as discussed above, overcomes any *prima facie* case of obviousness that could possibly be made based on the cited references.

Reconsideration and withdrawal of the rejection are respectfully requested.

IV. Claims 17, 33 and 34 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al., Lu et al. and Cho et al. and further in view of Davis et al. (Vaccine,

2000) and Chung et al. (Antivir. Chem Chemother., 2001 Abstract Only). Claims 17, 33 and 34 are canceled herein, rending the rejection moot.

V. Claims 4 and 18-20 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klinman et al., Lu et al. and Cho et al. and further in view of Hamour et al. (J. Infect., 1998 Abstract Only). Applicants respectfully disagree with this rejection as applied to these claims as amended.

A. The Prior Art Does Not Teach All of the Elements of the Claimed Methods

Klinman et al., Lu et al. and Cho et al. are discussed above, alone and in combination. Thus, there is nothing in Klinman et al., Lu et al. or Cho et al. alone or in any combination, that can be construed to teach the following elements:

1. Treatments to produce an immune response against a secondary infection in a subject that is immunocompromised as a result of an HIV or an SIV infection.
2. The production of an immune response to *Leishmania* in any subject (including immunocompromised subjects).
3. The use of a subset of immunostimulatory ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1, to induce the immune response in a immunocompromised subject.

The Hamour et al. abstract discloses that visceral Leishmania is an opportunistic infection in subjects with an HIV-1 infection. The Hamour et al. abstract describes treatment with amphotercin B, and suggest that amphoericin B could be used in combination therapeutics.

None of the cited references teaches the selection and administration of a subset of D-type ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from

4 to 1. While SEQ ID NO: 177 is one ODN that falls into the broad genus of D-type ODNs discussed in Klinman et al., the mere disclosure of this nucleic acid amongst hundreds of ODNs (both D and K type) does not provide any motivation to select and use this particular ODN.

In fact, it had been described in the art (see Raz) that K-type ODNs were effective for the treatment of *Leishmania*. Thus, upon combining these references, one of ordinary skill in the art would select and use one of the K-type ODNs described by Klinman et al.

B. The Documentation of an Unexpected Superior Result Overcomes a Prima Facie Case of Obviousness

Moreover, the documentation of unexpectedly superior results, as discussed above, overcomes any *prima facie* case of obviousness that could possibly be made based on the cited references. Macaques treated with the D ODNs developed significantly smaller lesions, and their infection did not progress over time. However, the severity of *Leishmania* infection in animals treated with immunostimulatory K ODNs (such as those described in Klinman et al.) was not significantly different than controls. Monkeys treated with D ODN had a 35-fold reduction in parasite burden at the lesion site. This effect of a subset of D-type ODNs that are at least 18 nucleotides to 30 nucleotides in length and that include a sequence represented by the formula: 5' $X_1X_2X_3$ Pu_1 Py_2 CpG Pu_3 Py_4 $X_4X_5X_6(W)_M(G)_N$-3' (SEQ ID NO : 22), wherein the central CpG motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 1, such as SEQ ID NO: 177 simply could not be predicted based on the cited prior art.

Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

It is respectfully requested that the amended claims submitted herewith should all be recombined and considered in the current case. The Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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